

## RELATIVE COSTS AND DISABILITY DUE TO DENGUE IN THAILAND: AN EPIDEMIOLOGICAL APPROACH

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Dengue virus infection is a global health problem with significant economic burden due to hospitalization and illness. This study evaluates the cost and disability adjusted life-years (DALYs) lost to symptomatic dengue in Kamphaeng Phet, Thailand, using data from a five-year prospective study in school children. All febrile school absences were evaluated, allowing comparison of dengue and non-dengue illnesses. Cost calculations include direct and indirect expenses. Dengue caused a loss of 398.5 DALYs/million (D/m) and \$20,110 from 1998-2002, representing 17.8% of all DALYs and 13.7% of dollars lost to febrile illness in the cohort. Yearly variability was observed, with maximum burden in the dengue epidemic years of 1998 and 2001 (710.9 D/m and \$5220, and 700 D/m and \$8600, respectively) and minimum in the interepidemic years of 2000 and 2002 (53.4 D/m and \$880, and 153 D/m and \$1870). The DALYs lost during epidemic years differed in clinical composition: while the majority of DALYs lost to dengue in 1998 were primarily in non-hospitalized patients (71.9%), the majority in 2001 were due to hospitalized illness (57.9%). DALYs lost to non-dengue illness were several-fold higher than for dengue each year; within hospitalized patients, however, dengue was responsible for greater loss of DALYs in all years but 2000. The average cost was higher for dengue compared to non-dengue febrile illness (\$64.50 vs. \$47.70). Considering dengue only, the average cost of illness was highest for hospitalized DHF patients, while total costs were higher for non-hospitalized dengue. The serotype-attributable burden of disease varied yearly: Den 3 was associated with the greatest costs and disability in 1998, Den 2 predominated from 1999-2002, and Den 4 was associated with minimal disease burden each year. These findings bear importance on the development of multivalent dengue vaccines. Dengue is associated with a significant amount of disability in the region (from 4-33% of DALYs lost to febrile illness each year), and should be given high priority in research and prevention efforts.

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## THE ROLE OF CELLULAR IMMUNITY IN DENGUE INFECTION

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Several studies have shown that prior infection with dengue virus increases the risk of developing severe disease with subsequent infection with another strain of the virus. Although some DHF (dengue hemorrhagic fever) cases occur with primary infection, over 90% of DHF cases occur in individuals who exhibit a secondary antibody response. In parallel with an enhanced humoral response in patients who develop DHF, cellular immunity also exhibits an enhanced activation

during a course of DHF. A prospective study of hospitalized patients suspected of having dengue infection has demonstrated that several immunological parameters were up-regulated in DHF compared to DF (dengue fever) patients. These include a cell surface activation marker; CD69 on CD8+ T cells and NK cells, cytokines such as IL-10, IFN- $\gamma$ , and soluble cytokine receptors. A recent study has shown that patients who sub-sequently developed severe dengue infection have more tumor necrosis factor secreting, dengue-specific CD8+ T cells in their peripheral blood than individuals who developed DF. Expansion of cross reactive CD8+ T cells during a secondary dengue infection has been demonstrated in a recent study. These observations suggest that stimulation of dengue specific T cells during a secondary infection may lead to the activation of various immune cells and cytokine cascades, resulting in inflammation and release of vasoactive substances which cause plasma leakage and coagulopathy.

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## **SPATIAL COHERENCE AND ASSOCIATION OF TEMPERATURE, RAINFALL AND THE INCIDENCE OF DENGUE HEMORRHAGIC FEVER IN THAILAND**

**Cummings DA, McDermott A, Endy TP, Nisalak A and Burke DS**

The seasonal increase in dengue hemorrhagic fever in Thailand is often cited as occurring concomitantly with the warm, rainy season. We have investigated this relationship in detail to determine if the seasonal variance in incidence is associated with seasonal variance in temperature and rainfall across Thailand. Using a time-series decomposition technique, the empirical mode decomposition, we examine the seasonal variance of DHF, rainfall and temperature in a large dataset describing monthly DHF incidence, mean monthly temperature and monthly rainfall in 41 provinces for 14 years. The empirical mode decomposition sifts time-series data into modes of different periodicities. Using the non-parametric spline covariance function, we find that temperature is synchronized across the country while DHF incidence and rainfall vary markedly in phase in different parts of the country. Phase coherence analysis of DHF incidence and rainfall suggests that the timing of the dengue season is linked to the timing of rainfall across Thailand. Additionally, we have found that annual DHF incidence rates are associated with higher mean annual temperatures. This relationship is modified by the distance from Bangkok, with provinces close to Bangkok varying little with varying temperature, while those furthest from Bangkok are more strongly associated with temperature. This modification of the effect of temperature suggests that several processes at different temporal and spatial scales affect incidence across the country.

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